

WHAT IS CLAIMED IS:

1. A method for treating a stroke, the method comprising:

(a) diagnosing a subject in need of treatment for a stroke; and

(b) administering to the subject a cyclooxygenase-2 selective

inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof

5 and a potassium ion channel modulator or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof.

2. The method of claim 1 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC<sub>50</sub> to COX-2 IC<sub>50</sub> not less than about 50.

3. The method of claim 1 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC<sub>50</sub> to COX-2 IC<sub>50</sub> not less than about 100.

4. The method of claim 1 wherein the cyclooxygenase-2 selective inhibitor is selected from the group consisting of celecoxib, deracoxib, valdecoxib, rofecoxib, lumiracoxib, etoricoxib, meloxicam, parecoxib, 4-(4-cyclohexyl-2-methyloxazol-5-yl)-2-fluorobenzenesulfonamide, 2-(3,5-difluorophenyl)-3-(4-(methylsulfonyl)phenyl)-2-cyclopenten-1-one, N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide, 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, 2-[(2,4-dichloro-6-methylphenyl)amino]-5-ethyl-benzeneacetic acid, (3Z)-3-[(4-chlorophenyl)[4-(methylsulfonyl)phenyl]methylene]dihydro-2(3H)-furanone, and (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid.

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5. The method of claim 1 wherein the potassium ion channel modulator is selected from the group consisting of dendrotoxin, dendrotoxin I, dendrotoxin K, alpha-dendrotoxin, beta-dendrotoxin, gamma-dendrotoxin, margatoxin, stichodactyla toxin, tityustoxin K, apamin, charylotoxin, clotrimazole, dequalinium chloride, iberiotoxin, kaliotoxin, neuropeptide Y, noxiustoxin, tolbutamide, chlorpropamide, glibenclamide, glipizide, nateglinide, repaglinide, glyburide, tolazamide, nicorandil, fampridine and penitrem A, or is a pharmaceutically acceptable salt or prodrug thereof.

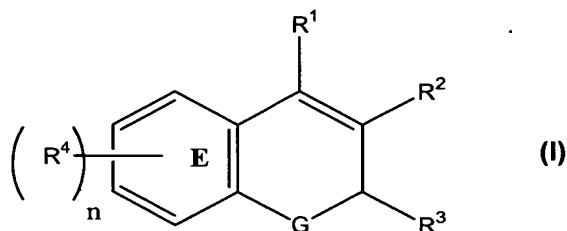
6. The method of claim 4 wherein the potassium ion channel modulator is selected from the group consisting of dendrotoxin, dendrotoxin I, dendrotoxin K, alpha-dendrotoxin, beta-dendrotoxin, gamma-dendrotoxin, margatoxin, stichodactyla toxin, tityustoxin K, apamin, charylotoxin, clotrimazole, dequalinium chloride,  
5 iberiotoxin, kaliotoxin, neuropeptide Y, noxiustoxin, tolbutamide, chlorpropamide, glibenclamide, glipizide, nateglinide, repaglinide, glyburide, tolazamide, nicorandil, fampridine and penitrem A, or is a pharmaceutically acceptable salt or prodrug thereof.

7. A method for treating a stroke, the method comprising:  
(a) diagnosing a subject in need of treatment for a stroke; and  
(b) administering to the subject a potassium ion channel modulator or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof and a  
5 cyclooxygenase-2 selective inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein the cyclooxygenase-2 selective inhibitor is a chromene compound, the chromene compound comprising a benzothiopyran, a dihydroquinoline or a dihydronaphthalene.

8. The method of claim 7 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC<sub>50</sub> to COX-2 IC<sub>50</sub> not less than about 50.

9. The method of claim 7 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC<sub>50</sub> to COX-2 IC<sub>50</sub> not less than about 100.

10. The method of claim 7 wherein the cyclooxygenase-2 selective inhibitor is a compound having the formula



wherein:

- 5            n is an integer which is 0, 1, 2, 3 or 4;  
             G is O, S or NR<sup>a</sup>;  
             R<sup>a</sup> is alkyl;  
             R<sup>1</sup> is selected from the group consisting of H and aryl;  
             R<sup>2</sup> is selected from the group consisting of carboxyl, aminocarbonyl,  
10   alkylsulfonylaminocarbonyl and alkoxycarbonyl;  
             R<sup>3</sup> is selected from the group consisting of haloalkyl, alkyl, aralkyl,  
             cycloalkyl and aryl optionally substituted with one or more radicals selected from  
             alkylthio, nitro and alkylsulfonyl; and  
             each R<sup>4</sup> is independently selected from the group consisting of H, halo,  
15   alkyl, aralkyl, alkoxy, aryloxy, heteroaryloxy, aralkyloxy, heteroaralkyloxy, haloalkyl,  
             haloalkoxy, alkylamino, arylamino, aralkylamino, heteroarylamino,  
             heteroarylalkylamino, nitro, amino, aminosulfonyl, alkylaminosulfonyl,  
             arylaminosulfonyl, heteroarylaminosulfonyl, aralkylaminosulfonyl,  
             heteroaralkylaminosulfonyl, heterocyclosulfonyl, alkylsulfonyl, hydroxyarylcarbonyl,  
20   nitroaryl, optionally substituted aryl, optionally substituted heteroaryl, aralkylcarbonyl,  
             heteroarylcarbonyl, arylcarbonyl, aminocarbonyl, and alkylcarbonyl; or R<sup>4</sup> together  
             with the carbon atoms to which it is attached and the remainder of ring E forms a  
             naphthyl radical.

11.    The method of claim 7 wherein the cyclooxygenase-2 selective inhibitor is (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid.

12.    The method of claim 7 wherein the potassium ion channel modulator is selected from the group consisting of dendrotoxin, dendrotoxin I, dendrotoxin K, alpha-dendrotoxin, beta-dendrotoxin, gamma-dendrotoxin, margatoxin, stichodactyla toxin, tityustoxin K, apamin, charylotoxin, clotrimazole, dequalinium chloride,  
5   iberiotoxin, kaliotoxin, neuropeptide Y, noxiustoxin, tolbutamide, chlorpropamide, glibenclamide, glipizide, nateglinide, repaglinide, glyburide, tolazamide, nicorandil, fampridine and penitrem A, or is a pharmaceutically acceptable salt or prodrug thereof.

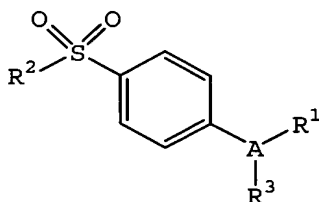
13.    A method for treating a stroke, the method comprising:

- (a) diagnosing a subject in need of treatment for a stroke; and  
(b) administering to the subject a potassium ion channel modulator or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof and a  
5 cyclooxygenase-2 selective inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein the cyclooxygenase-2 selective inhibitor is a tricyclic compound, the tricyclic compound containing a benzenesulfonamide or methylsulfonylbenzene moiety.

14. The method of claim 13 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC<sub>50</sub> to COX-2 IC<sub>50</sub> not less than about 50.

15. The method of claim 13 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC<sub>50</sub> to COX-2 IC<sub>50</sub> not less than about 100.

16. The method of claim 13 wherein the cyclooxygenase-2 selective inhibitor is a compound of the formula:



5 wherein:

A is selected from the group consisting of partially unsaturated or unsaturated heterocyclyl and partially unsaturated or unsaturated carbocyclic rings;

R<sup>1</sup> is selected from the group consisting of heterocyclyl, cycloalkyl, cycloalkenyl and aryl, wherein R<sup>1</sup> is optionally substituted at a substitutable position  
10 with one or more radicals selected from alkyl, haloalkyl, cyano, carboxyl, alkoxycarbonyl, hydroxyl, hydroxyalkyl, haloalkoxy, amino, alkylamino, arylamino, nitro, alkoxyalkyl, alkylsulfinyl, halo, alkoxy and alkylthio;

R<sup>2</sup> is selected from the group consisting of methyl and amino; and

R<sup>3</sup> is selected from the group consisting of H, halo, alkyl, alkenyl,  
15 alkynyl, oxo, cyano, carboxyl, cyanoalkyl, heterocycloxy, alkyloxy, alkylthio, alkylcarbonyl, cycloalkyl, aryl, haloalkyl, heterocyclyl, cycloalkenyl, aralkyl,

heterocyclalkyl, acyl, alkylthioalkyl, hydroxyalkyl, alkoxyalkyl, arylalkyl, aralkylalkyl, aralkenyl, alkoxyalkyl, arylthioalkyl, aryloxyalkyl, aralkylthioalkyl, aralkoxyalkyl, alkoxyaralkoxyalkyl, alkoxyalkylalkyl, aminocarbonyl, aminocarbonylalkyl, alkylaminocarbonyl, N- arylaminocarbonyl, N-alkyl-N- arylaminocarbonyl, alkylaminocarbonylalkyl, carboxyalkyl, alkylamino, N-aryl amino, N-aralkylamino, N-alkyl-N-aralkylamino, N-alkyl-N-aryl amino, aminoalkyl, alkylaminoalkyl, N-arylaminomethyl, N-aralkylaminomethyl, N-alkyl-N-aralkylaminomethyl, N-alkyl-N-arylaminomethyl, aryloxy, aralkoxy, arylthio, aralkylthio, alkylsulfonyl, alkylsulfonyl, aminosulfonyl, alkylaminosulfonyl, N-arylaminosulfonyl, arylsulfonyl, and N-alkyl-N-arylaminosulfonyl.

17. The method of claim 13 wherein the cyclooxygenase-2 selective inhibitor is selected from the group consisting of celecoxib, valdecoxib, parecoxib, deracoxib, rofecoxib, etoricoxib, and 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

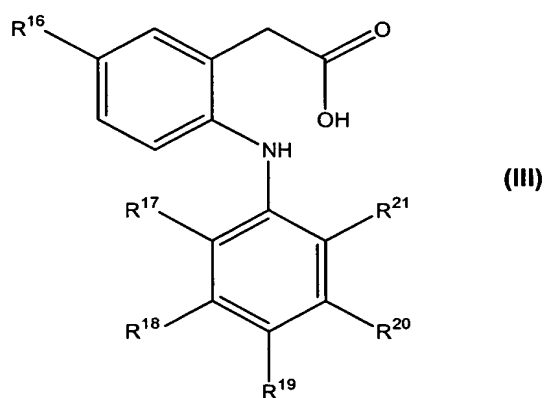
18. The method of claim 13 wherein the potassium ion channel modulator is selected from the group consisting of dendrotoxin, dendrotoxin I, dendrotoxin K, alpha-dendrotoxin, beta-dendrotoxin, gamma-dendrotoxin, margatoxin, stichodactyla toxin, tityustoxin K, apamin, charylotoxin, clotrimazole, dequalinium chloride, iberiotoxin, kaliotoxin, neuropeptide Y, noxiustoxin, tolbutamide, chlorpropamide, glibenclamide, glipizide, nateglinide, repaglinide, glyburide, tolazamide, nicorandil, fampridine and penitrem A, or is a pharmaceutically acceptable salt or prodrug thereof.

19. A method for treating a stroke, the method comprising:  
(a) diagnosing a subject in need of treatment for a stroke; and  
(b) administering to the subject a potassium ion channel modulator or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof and a cyclooxygenase-2 selective inhibitor or an isomer, a pharmaceutically acceptable salt, ester, or prodrug thereof, wherein the cyclooxygenase-2 selective inhibitor is a phenyl acetic acid compound.

20. The method of claim 19 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC<sub>50</sub> to COX-2 IC<sub>50</sub> not less than about 50.

21. The method of claim 19 wherein the cyclooxygenase-2 selective inhibitor has a selectivity ratio of COX-1 IC<sub>50</sub> to COX-2 IC<sub>50</sub> not less than about 100.

22. The method of claim 19 wherein the cyclooxygenase-2 selective inhibitor is a compound having the formula:



wherein:

R<sup>16</sup> is methyl or ethyl;

R<sup>17</sup> is chloro or fluoro;

R<sup>18</sup> is hydrogen or fluoro;

R<sup>19</sup> is hydrogen, fluoro, chloro, methyl, ethyl, methoxy, ethoxy or

hydroxy;

R<sup>20</sup> is hydrogen or fluoro; and

R<sup>21</sup> is chloro, fluoro, trifluoromethyl or methyl; and provided that each of R<sup>17</sup>, R<sup>18</sup>, R<sup>19</sup> and R<sup>20</sup> is not fluoro when R<sup>16</sup> is ethyl and R<sup>19</sup> is H.

23. The method of claim 22 wherein:

R<sup>16</sup> is ethyl;

R<sup>17</sup> and R<sup>19</sup> are chloro;

R<sup>18</sup> and R<sup>20</sup> are hydrogen; and

R<sup>21</sup> is methyl.

24. The method of claim 19 wherein the potassium ion channel modulator is selected from the group consisting of dendrotoxin, dendrotoxin I, dendrotoxin K, alpha-dendrotoxin, beta-dendrotoxin, gamma-dendrotoxin, margatoxin, stichodactyla toxin, tityustoxin K, apamin, charylotoxin, clotrimazole, dequalinium chloride,  
5 iberiotoxin, kaliotoxin, neuropeptide Y, noxiustoxin, tolbutamide, chlorpropamide, glibenclamide, glipizide, nategliniide, repagliniide, glyburide, tolazamide, nicorandil, fampridine and penitrem A, or is a pharmaceutically acceptable salt or prodrug thereof.

25. A method for treating a stroke, the method comprising:  
(a) diagnosing a subject in need of treatment for a stroke; and  
(b) administering to the subject a cyclooxygenase-2 selective inhibitor selected from the group consisting of celecoxib, deracoxib, valdecoxib,  
5 rofecoxib, lumiracoxib, etoricoxib, parecoxib, 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone, and (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid; and a potassium ion channel modulator is selected from the group consisting of dendrotoxin, dendrotoxin I, dendrotoxin K, alpha-dendrotoxin, beta-dendrotoxin, gamma-dendrotoxin,  
10 margatoxin, stichodactyla toxin, tityustoxin K, apamin, charylotoxin, clotrimazole, dequalinium chloride, iberiotoxin, kaliotoxin, neuropeptide Y, noxiustoxin, tolbutamide, chlorpropamide, glibenclamide, glipizide, nategliniide, repagliniide, glyburide, tolazamide, nicorandil, fampridine and penitrem A, or is a pharmaceutically acceptable salt or prodrug thereof.

15 26. The method of claim 25 wherein the cyclooxygenase-2 selective inhibitor is celecoxib.

27. The method of claim 25 wherein the cyclooxygenase-2 selective inhibitor is deracoxib.

28. The method of claim 25 wherein the cyclooxygenase-2 selective inhibitor is valdecoxib.

29. The method of claim 25 wherein the cyclooxygenase-2 selective inhibitor is rofecoxib.

30. The method of claim 25 wherein the cyclooxygenase-2 selective inhibitor is etoricoxib.

31. The method of claim 25 wherein the cyclooxygenase-2 selective inhibitor is parecoxib.

32. The method of claim 25 wherein the cyclooxygenase-2 selective inhibitor is 2-(3,4-difluorophenyl)-4-(3-hydroxy-3-methylbutoxy)-5-[4-(methylsulfonyl)phenyl]-3(2H)-pyridazinone.

33. The method of claim 25 wherein the cyclooxygenase-2 selective inhibitor is (S)-6,8-dichloro-2-(trifluoromethyl)-2H-1-benzopyran-3-carboxylic acid.

34. The method of claim 25 wherein the cyclooxygenase-2 selective inhibitor is lumiracoxib.

35. The method of claim 1 wherein the stroke is a hemorrhagic stroke.

36. The method of claim 1 wherein the stroke is an ischemic stroke.